Machine Learning Pins Down Novel Antimicrobial Peptides

By YAN Fusheng (Staff Reporter)

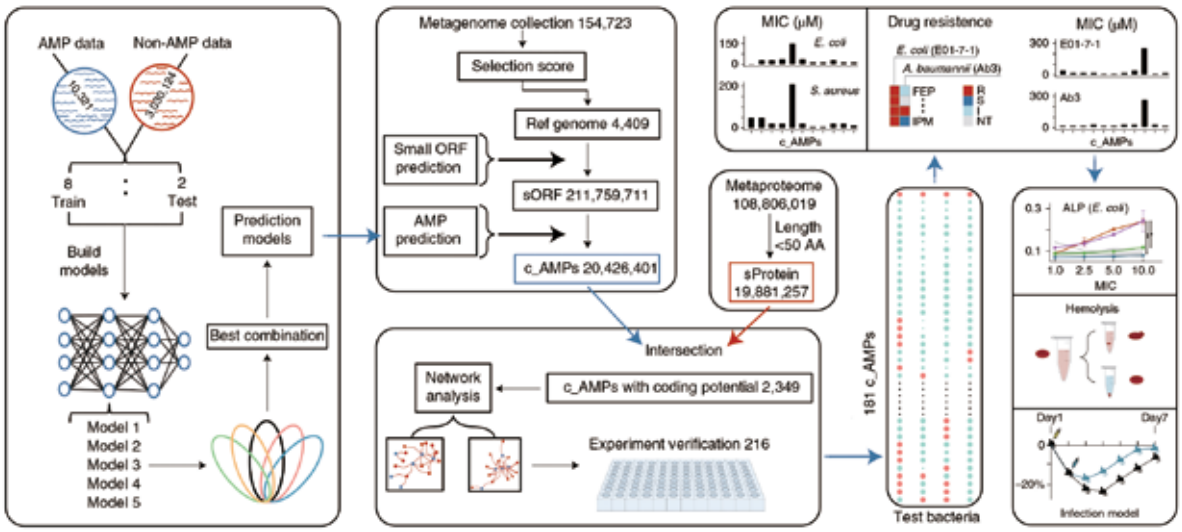
Antibiotic-resistant pathogens pose a severe threat to global health. Under the premise of lacking new classes of antimicrobial drugs, the death toll of untreatable infections is projected to reach 10 million annually by 2050.

Antimicrobial peptides (AMPs) – small proteins typically 8~50 amino acids in length that confer protection against pathogens – are an established and promising alternative to traditional antibiotics because they are less likely to elicit resistance. However, only a limited number of these molecules have entered clinical practice. High-throughput approaches using microbiome data that widen the search for promising AMPs may provide a new source of candidates to add up the number.

Reported in *Nature Biotechnology*, Ma *et al*. from the CAS Institute of Microbiology described a clever artificial intelligence (AI) strategy to identify new antibiotics.

They used natural language processing tools to effectively mine large human gut microbiome datasets in search of AMPs. This very strategy contributes to emerging research that may revolutionize antibiotic discovery, shifting it from traditional methods that rely on arduous trial-and-error experimentation into a new era when molecules can be rapidly picked out by computer.

Trawling through large-scale metagenomics data, they identified 241 candidate sequences that resembled known AMPs. Then, they chemically synthesized these candidate peptides and assessed their antimicrobial activity *in vitro*.



Schematic workflow for computer-based antibiotic discovery. (Credit: Ma *et al./Nature Biotechnology*)

Of the 241 peptides, Ma *et al*. were able to synthesize 216, and 181 of these were found to exert antimicrobial activities, leading to a hit rate of 83.8%. The researchers then assessed the similarity of the 181 peptides with known AMP sequences present in the training set, revealing that the highest identity was just 61.4%, with most sequences having identities of less than 40%. This analysis indicates that this AI-based strategy can pin down peptides whose sequences, or action mechanisms, are distinct from that of conventional AMPs.

"Indeed, in our training dataset, we used solely the sequence information of experimentally verified AMPs, and, yet, our approach managed to detect deep, hidden features within them and consequently discovered diverse AMPs in metagenomes," said the authors.

The researchers eventually selected three peptides of low toxicity in assays using human cells and confirmed their effectiveness against typical lung bacterial infection by *K. pneumoniae* in a mouse model, showing that peptide treatment reduced bacterial load by >10-fold.

Collectively, they presented an AI approach based on natural language processing and deep learning to identify novel peptide antibiotics from human gut microbiome data.

"Platforms such as the one described here are likely to transform antimicrobial research, making it possible to discover a greater variety of potential antibiotics in record time," commented Dr. Cesar de la Fuente-Nunez, whose researches interface bioengineering and computer science. "As this study demonstrates, AI approaches hold promise for the discovery of much-needed antimicrobial drugs, which can help to replenish our depleted arsenal."

References

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